47. (new)A composition comprising:

(-) 3-[4-[2-phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine 0.353%

Lactose	87.65 %
Polyethylene glycol 6000	7 %
Talc	5 %

48. (new)A composition comprising:

(-) 3-[4-[2-phenoxazin-10-yl)ethoxy]phenyl-2-ethoxypropanoic acid, arginine 7.075%

Lactose	80.95%
Polyethylene glycol 6000	7 %
Talc	5 %

REMARKS

Claims 1-25 are pending in the above-referenced application. These claims have been cancelled. New claims 26-48 has been added to more distinctly claim that which Applicants regard as the invention. New claims 26 and 27 correspond to prior claims 4 and 5. Claim 28 recites a specific embodiment. New claims 29-48 generally correspond to prior claims 6-25.

1. The Rejections Under 35 U.S.C. §112

Claims 1, 4-6, 11-12, 19 and 22 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted that the term "low water content" in claims 4, 6, 11 and 12 is a relative term, which renders the claim indefinite; that the term "(very) low water content" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention;

that the terms "low (water) vapor pressure" and "low oxygen pressure" in claims 5 and 19 are indefinite because it does not provide the exact extent or level of pressure required for the steps to be carried out in the process for the preparation.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claims 1-25 have been cancelled. New claims 26-48 have been added. New claim 26 recites that the mixture is compressed with excipients of a water content below about 1%; claim 27 recites that the steps are carried out at water vapour pressure below about 40% and oxygen pressure below about 10%; claim 29 recites that the composition comprises pharmaceutically acceptable excipients with water content below about 1% and an antioxidant. New claims 26, 27 and 29 are supported by the specification on page 4, lines 24-26 and page 5, lines 23-25.

It is further asserted that the term "Tablettose" in claim 22 is indefinite because it is confusing and unclear as to whether one of ordinary skill in the art would recognize theterm. The Examiner has requested Applicant to provide some form of literature in which the Examiner is able to determine the patentability of the invention being made. In response, Applicants herewith submit as Appendix A, pages 252-254 from Handbook of Pharmaceutical of Excipients, Ainley Wade and Paul Weller, eds., 2nd Edition, 1994, ISBN 0 91730 66 8, where "Tablettose" is described. Essentially, Tablettose is lactose monohydrate. In view of new claims 26-48 and the above arguments, Applicants assert that the rejections under 35 U.S.C. §112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

2. The Rejections Under 35 U.S.C. §103

Claims 1-25 have been rejected under 35 U.S.C. §103 as being unpatentable over Hulin in view of Alvarez et al. Specifically, the Examiner states:

> Hulin teaches a pharmaceutical composition in the form of a tablet, powder of capsule comprising propionic acid derivatives or their pharmaceutically acceptable salts, in combination with a pharmaceutically acceptable carrier for

use in the treatment of hypoglycemia and hypercholesterolemia associated with diabetes (see reference column 1, lines 15-47); (column 5, lines 7-40); (column 11, lines 41-68); column 12, lines 1-25) and see examples. The composition is provided in blood glucose lowering effective amount. Furthermore, additional components such as flavorants, sweeteners and explicitly disclose the use of an antioxidant in his formulation. It is the position of the Examiner that one of the ordinary skill in the art would include an antioxidant agent or preservative in their formulation to prevent oxidation or degradation of a compound composition. Such skill is also evident from the reference of Alvarez et al.

Alvarez et al. disclose a pharmaceutical composition comprising propionic acid derivatives and their pharmaceutically acceptable salts for oral administration wherein the tablet composition can comprise an antioxidant, such as tocopherol acetate (vitamin E) and the like. In addition, various excipients, fillers, disintegrants, lubricants, flavoring agents and coloring agents can also be formulated in the composition. The additives disclosed, for example, are microcrystalline cellulose, starch, pregelatinized starch, lactose, magnesium stearate, stearic acid, talc and colloidal silica (see entire reference, especially column 3, lines 45-60) and (see examples).

Therefore, it would have been obvious to one of ordinary skill in the art of the time the invention was made to use the formulation of Alvarez et al. with Hulin to obtain a stabilized pharmaceutically composition, comprising propionic acids and their acceptable salts in combination with antioxidants, with the expected results of the highly effective oral composition, enhanced by decreased oxidation for use in the treatment of diabetes.

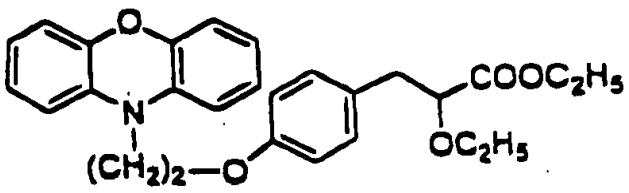
Instant claims 20-25, provide for specified percentages. There is no criticality seen in the specified ratios of the additives and excipients. [(The prior art teaches the generic concept of including such ingredients (excipients, additives,

fillers, lubricants)] and it is deemed obvious that one of the ordinary skill in the pharmaceutical art would determine suitable percentages through routine and conventional experimentation

Applicant respectfully traverses the rejection. *Contra* to the Examiner's assertion, it would not have been obvious to use the formulation of Alvarez et al. with Hulin to obtain a stabilized pharmaceutical composition, comprising propionic acids and their acceptable salts in combination with antioxidants, with the expected result of a highly effective composition for a number of reasons.

First, there was no suggestion in either of the cited references of formulating compositions with water content of below 1%. There was actually no concern expressed in either of the recited references regarding mixing the active ingredient with excipients having a water content of below about 1%. It is stated in Hulin that the composition may be in liquid or solid form; it is not suggested that it would be advantageous for it to be in solid form. In columns 22 and 23 of Alvarez, water is used in formulating tablets. Use of water will destabilize the composisition. Furthermore, there was no suggestion in either reference regarding the advantages of formulating a composition with a low water content and obtaining the composition optionally under low vapour pressure and oxygen pressure.

Second, Applicants note that the structures of the compounds encompassed by Hulin and Alvarez are very different from (-) 3-[4-[2-phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid. For Examiner's reference, the structure of (-) 3-[4-[2-phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid is shown below.



Columns 3 and 4 of Hulin and columns 1 and 2 of Alvarez are attached hereto as Appendix B. The compounds of Hulin and Alvarez do not contain a phenoxazine ring and would thus presumably have very different properties. Therefore, to one of ordinary skill in the art, it would not be obvious that various salts and excipients that could be used to formulate the compositions of Hulin and Alvarez could be used to obtain the compositions of the present invention. Given the differences between the compounds disclosed in Hulin and Alvarez and (-) 3-[4-[2-phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, it would not be obvious to combine the disclosures of Hulin and Alvarez to obtain the compositions of the present invention.

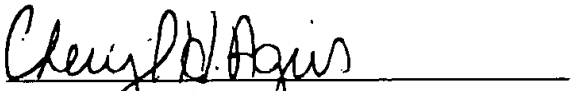
In view of the above arguments, Applicants assert that the rejections under 35 U.S.C. §103 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

4. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact Cheryl H. Agris by telephone at (914) 712-0093 if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: 9/27/02



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Counsel for
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APPENDIX A

Lactose

1. Nonproprietary Names

BP: Lactose monohydrate
PhEur: Lactosum
USPNF: Lactose monohydrate
Note that the USPNF XVII (Suppl 9) also contains a monograph for anhydrous lactose, see Sections 9 and 19.

2. Synonyms

Fast-Flo; 4-(β-D-galactosido)-D-glucose; *Lactochem*; *Microtose*; milk sugar; *Pharmatose*; saccharum lactis; *Tablettose*; *Zeparox*.

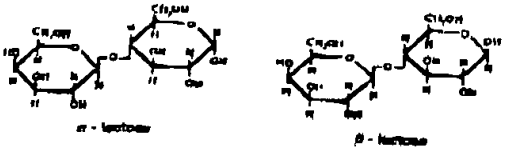
3. Chemical Name and CAS Registry Number

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous [63-42-3]
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

4. Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$C_{12}H_{22}O_{11}$	342.30 (anhydrous)
$C_{12}H_{22}O_{11}.H_2O$	360.31 (monohydrate)

5. Structural Formula



α-lactose β-lactose

6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets, capsules, and to a more limited extent in lyophilized products and infant food formulas.[1-15]

Spray-dried lactose was first developed over 30 years ago for use in solid dosage pharmaceutical formulations. Today, many other lactose grades are commercially available, including anhydrous α-lactose, α-lactose monohydrate, and to a minor extent, anhydrous β-lactose.

Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct compression grades are often used to carry small quantities of drug and this permits tablets to be made without granulating.

Direct compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and are generally composed of spray-dried lactoses which contain specially prepared pure α-lactose monohydrate along with a small amount of amorphous lactose. The amorphous lactose improves the compression force/hardness profile of the lactose. Other specially produced direct compression grades of lactose do not contain amorphous material but may contain glassy or vitreous areas which impart improved compressibility. Direct compression grades of lactose may also be combined with microcrystalline cellulose or starch, and usually require a tablet lubricant such as 0.5% w/w magnesium stearate. The use of direct compression grades of lactose results in tablets of higher breaking strength than standard lactose. Concentrations of lactose generally used in these formulations are from 65–85%.

Various lactose grades are commercially available which have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application, e.g. the particle size range selected for capsules is often dependent upon the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include as a carrier/diluent for inhalation products and in lyophilized products where lactose is added to freeze-dried solutions to increase plug size and aid caking. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

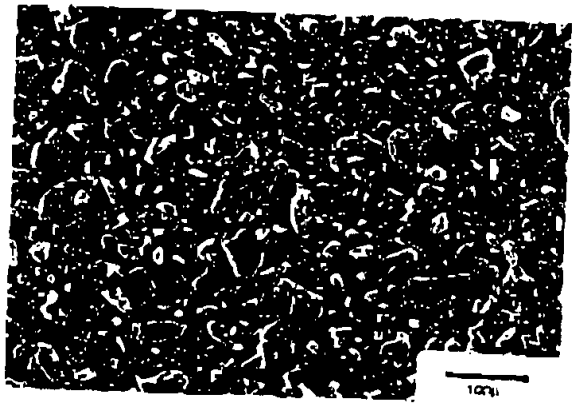
8. Description

White to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than the α-form.

Several different forms of lactose are commercially available; anhydrous α-lactose, α-lactose monohydrate, and to a lesser extent, anhydrous β-lactose which typically contains 70% anhydrous β-lactose and 30% anhydrous α-lactose, although grades containing a greater quantity of anhydrous β-lactose are also available, e.g. *Pharmatose DCL 21* (DMV International). α-Lactose may also contain a small quantity of the β-form.

SEM: 1
Subject: Lactose monohydrate (*Lactose D30*)
Manufacturer: Meggle GmbH

SEM: 2
Excipient: Lactose monohydrate (*Lactose G300*)
Manufacturer: Meggle GmbH

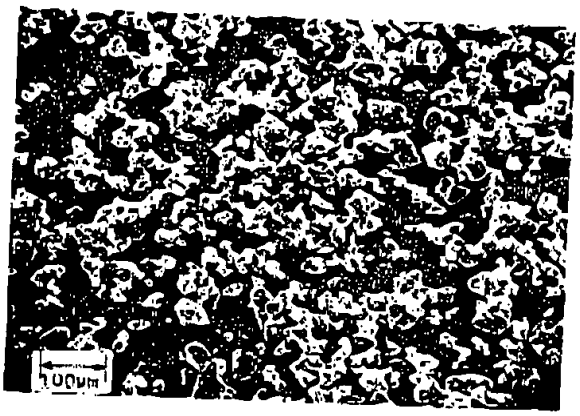


SEM: 3
Excipient: Lactose monohydrate (*Tablettose*)
Manufacturer: Meggle GmbH

SEM: 4
Excipient: Lactose monohydrate (*Lactose anhydrate 60M*)
Manufacturer: Quest International Inc (Sheffield Products)
Lot No.: 8A-13 (9 NJ 16)
Magnification: 120x
Voltage: 20 kV

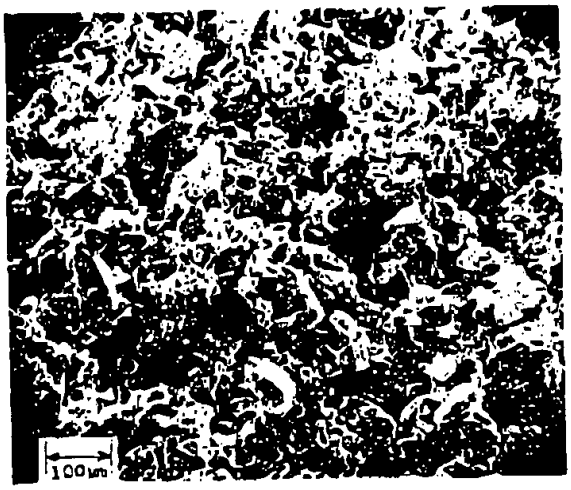
SEM: 5
Excipient: Lactose monohydrate (*Lactose monohydrate 80S*)
Manufacturer: Quest International Inc (Sheffield Products)
Lot No.: 8A-12 (9 NK 18)
Magnification: 120x
Voltage: 20 kV

SEM: 6
Excipient: Lactose monohydrate (*Lactose monohydrate 80M*)
Manufacturer: Quest International Inc (Sheffield Products)
Lot No.: 8A-11 (9 NJ 18)
Magnification: 120x
Voltage: 20 kV



SEM: 7
Excipient: Lactose monohydrate (*Lactose monohydrate crystallized*)
Manufacturer: Quest International Inc (Sheffield Products)
Lot No.: SRA-10 (9 NL 20)
Magnification: 120x
Voltage: 20 kV

SEM: 8
Excipient: Lactose monohydrate (*Lactose monohydrate impalpable*)
Manufacturer: Quest International Inc (Sheffield Products)
Lot No.: SRA-14 (9 NH 22)
Magnification: 120x
Voltage: 20 kV



9. Pharmacopeial Specifications

Test	PhEur 1994	USPNF XVII (Suppl 9)
Identification	+	+
Appearance of solution	+	+
Specific rotation (anhydrous basis)	+54.4° to +55.9°	+54.8° to +55.5°
Microbial limits	100/g	100/g
Acidity or alkalinity	+	+
Loss on drying		
Anhydrous form	—	≤ 0.1%
Monohydrate	—	≤ 0.5%
Water		
Anhydrous form	—	≤ 1.0%
Monohydrate	4.5-5.5%	4.5-5.5%
Residue on ignition	—	≤ 0.1%
Sulfated ash	≤ 0.1%	—
Heavy metals	≤ 5 ppm	≤ 5 ppm
Organic volatile impurities		+
Protein and light-absorbing impurities	+	+

10. Typical Properties

Angle of repose: *see* Table I.
Compressibility: *see* HPE Data.
Density:
1.540 for α-lactose monohydrate;
1.589 for anhydrous β-lactose.
Density (bulk): *see* Table I and HPE Data.
Density (tapped): *see* Table I and HPE Data.
Flowability: *see* HPE Data.
Hygroscopicity: lactose monohydrate is stable in air and is unaffected by humidity at room temperature. However, the amorphous form, depending upon how it is dried, may be affected by humidity and can be converted to the monohydrate. *See also* HPE Data.
Melting point:
201-202°C for α-lactose monohydrate;
223°C for anhydrous α-lactose;
252.2°C for anhydrous β-lactose.
Moisture content: anhydrous lactose normally contains up to 1% w/w water. Lactose monohydrate contains approximately 5% w/w water of crystallization and normally ranges between 4.5-5.5% w/w water content. *See also* Table I and HPE Data.
Osmolarity: a 9.75% w/v aqueous solution is iso-osmotic with serum.
Particle size distribution: *see* Table II.
Solubility:

Solvent	Solubility at 25°C Unless otherwise stated
Chloroform	practically insoluble
Ethanol	practically insoluble
Ether	practically insoluble
Water	1 in 4.63
	1 in 3.14 at 40°C
	1 in 2.04 at 50°C
	1 in 1.68 at 60°C
	1 in 1.07 at 80°C

Specific rotation $[\alpha]_D^{20}$: +54.8° to +55.5° for anhydrous lactose, as a 10% w/v aqueous solution.

Table 1: Typical physical properties of selected commercially available lactoses.

Supplier/Grade	Angle of repose (°)	Density (g/cm³) Bulk	Density (g/cm³) Tapped	Specific surface area (m²/g)	Water content (%)
Borculo Whey Products (Lactochem)					
Microfine	—	—	—	—	≤ 5.5
Zeparex[a]	—	0.6-0.7	—	—	≤ 5.5
DMV International					
Pharmatose 50M	36	0.80	0.95	—	5.2
Pharmatose 80M	38	0.76	0.91	—	5.2
Pharmatose 90M	39	0.76	0.91	—	5.2
Pharmatose 100M	39	0.75	0.90	—	5.2
Pharmatose 110M	40	0.73	0.89	—	5.2
Pharmatose 125M	44	0.68	0.87	—	5.2
Pharmatose 150M	—	0.58	0.89	0.45	5.2
Pharmatose 200M	—	0.55	0.85	0.50	5.2
Pharmatose 325M	48	0.67	0.84	—	5.2
Pharmatose 350M	—	0.50	0.82	0.60	5.2
Pharmatose 450M	—	0.47	0.77	1.0	5.2
Pharmatose DCL 11[b]	31	0.61	0.73	—	4.8
Pharmatose DCL 21[c]	39	0.67	0.83	0.35	0.5
Foremost Ingredients Group					
Inspalpable #312	—	0.53	0.81	—	4.8-5.2
Inspalpable #313	—	0.48	0.78	—	4.8-5.2
Spray Powder #315	—	0.67	0.78	—	4.8-5.2
Fast-Flo #316	—	0.58	0.70	—	4.8-5.2
Meggle GmbH					
Lactose D10	35	0.50	0.59	—	5.1
Lactose D30	33	0.59	0.68	—	5.1
Lactose D50	34	0.72	0.85	—	5.1
Lactose GK	—	0.72	0.87	—	5.1
Lactose G200	—	0.46	0.51	—	5.1
Microtose	—	0.34	0.41	—	5.1
Tablettose	32	0.53	0.65	—	5.1
Quest International Inc (Sheffield Products)					
Monohydrate 60S	—	—	—	—	≤ 5.5
Monohydrate 80S	—	—	—	—	≤ 5.5
Monohydrate 80M	—	—	—	—	≤ 5.5
Monohydrate Capsulating	—	—	—	—	≤ 5.5
Monohydrate Impalpable	—	—	—	—	≤ 5.5
Anhydrous Direct Tableting	—	—	—	—	≤ 1.0
Anhydrous 60M	—	—	—	—	≤ 1.0
Anhydrous 80M	—	—	—	—	≤ 1.0
Anhydrous Impalpable	—	—	—	—	≤ 1.0

Note:
a. Direct compression grade of lactose.
b. Spray-dried lactose monohydrate.
c. Anhydrous lactose containing 82% β-lactose.
Unless otherwise noted all of the above grades are α-lactose monohydrate.

[redacted]

APPENDIX B

PHARMACEUTICAL COMPOSITION

This is a continuation of U.S. patent application Ser. No. 07/780,664, filed Oct. 18, 1991, which is now abandoned which is a continuation-in-part of Ser. No. 07/683,663 filed Apr. 15, 1991, now abandoned.

TECHNICAL FIELD

A pharmaceutical composition is disclosed for peptidomimetic compounds which are inhibitors of renin. In particular, the composition comprises a tablet comprising the renin inhibitor and a pharmaceutically acceptable organic polycarboxylic acid. The tablet can also comprise one or more pharmaceutically acceptable non-ionic surfactants.

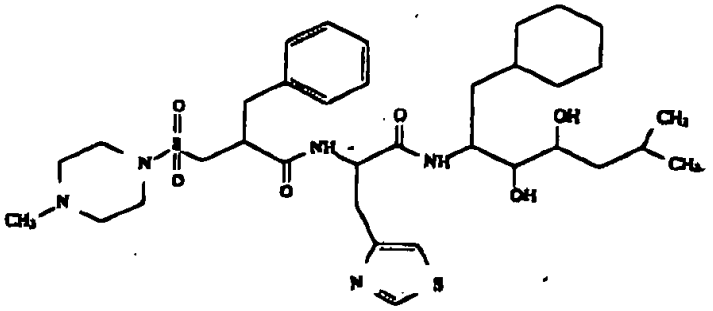
BACKGROUND OF THE INVENTION

The ability to orally administer peptide or peptide-like therapeutic agents has been a long-standing goal of pharmaceutical research. For example, many efforts have been made to develop an oral dosage form for insulin. Unfortunately, these efforts have been unsuccessful.

Properties which make peptides difficult to administer orally include their susceptibility to enzymatic degradation in the digestive tract and the fact that some peptides are not readily transported from the digestive system into the blood stream. As a result of these problems, it is difficult to achieve desired blood levels of peptides or peptide-like therapeutic agents with relatively low oral doses and a relatively low number of oral doses per day.

Methods used to overcome the ability of peptides to be enzymatically degraded and to improve absorption into the blood stream from the digestive tract have included making analogs which are less peptide-like in structure and which are reduced in size (i.e., molecular weight). Such methods are deemed to be successful when the peptide analog achieves satisfactory blood levels after oral administration.

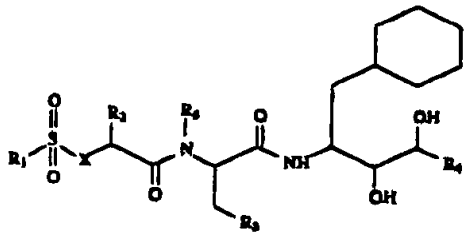
The above-mentioned techniques have been applied to preparing analogs of the peptide substrate of the enzyme renin. Small, peptide-like molecules have been prepared which show efficacy in lowering blood pressure. For example, compound I (shown below) reduces blood pressure in salt depleted dogs after oral or intravenous administration. However, the bioavailability on oral dosing (to fasted dogs) of salts of compound I as a standard tablet or powder filled capsule compositions (see Example 12, compositions S1-S5) is about 9 to 44%. To be able to administer the compound at the lowest possible dose and lowest frequency of dosing, it would be preferrable if the oral bioavailability of compound I and its pharmaceutically acceptable salts was higher than that exhibited by the conventional tablets and powder filled capsules mentioned above.



(I)

DISCLOSURE OF THE INVENTION

In accordance with the present invention there is a pharmaceutical tablet composition comprising a compound of the formula (II):



(II)

wherein

R_1 is 4-piperazinyl, 1-methyl-4-piperazinyl, 1-methyl-1-oxo-4-piperazinyl, 2-oxo-4-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl or 1-methyl-4-homopiperazinyl;

R_2 is benzyl, p-methoxybenzyl, 2-phenylethyl, 1-naphthylmethyl or 2-naphthylmethyl;

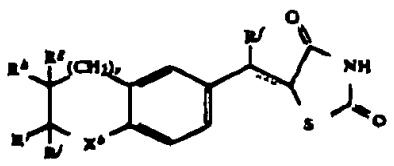
R_3 is 4-thiazolyl, 2-amino-4-thiazolyl, 2-thiazolyl, 5-thiazolyl, 1-pyrazolyl, 3-pyrazolyl, 1-imidazolyl, n-propyl, isopropyl, CH_3S— or CH_3SCH_2—;

R4 is loweralkyl or cyclopropyl;

R_5 is hydrogen or loweralkyl; and

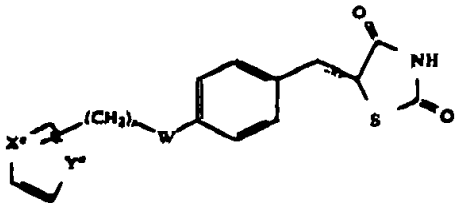
X is CH_2 or NH; or a pharmaceutically acceptable salt, ester or prodrug thereof, and a pharmaceutically acceptable organic polycarboxylic acid. In addition, the tablet composition can further comprise one or more pharmaceutically acceptable non-ionic surfactants. When formulated as a tablet comprising a pharmaceutically acceptable organic polycarboxylic acid or a pharmaceutically acceptable organic polycarboxylic acid and one or more pharmaceutically acceptable non-ionic surfactants, the compound of formula (II)

Eggler et al., U.S. Pat. No. 4,703,052, disclose hypoglycemic thiazolidinediones of the formula



where the dotted line represents an optional bond, R^f is H, methyl or ethyl, X^b is O, S, SO, SO_2, CH_2, CO, CHOH or NR^k, R^k is H or an acyl group and the numerous definitions of R^g, R^h, R^i and R^j include R^g, R^h and R^i as hydrogen or methyl and R^j as optionally substituted phenyl, benzyl, phenethyl or styryl. EP 283,035A and EP 299,620A describe structurally related benzoxazole and benzofuran derivatives as antidiabetic agents.

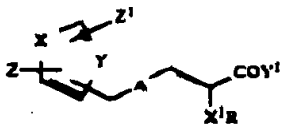
Clark et al., in published World patent applications WO89/08650, WO89/8651 and WO89/08652 disclose hypoglycemic thiazolidinediones which collectively include compounds of the type:



wherein ——— represents a bond or no bond; W is O, CO, CH_2, CHOH, or —CH=CH—; s is 0, 1 or 2; X^a is S, O, NR^a, —CH=CH—, —CH=N— or —N=CH—; and Y^a is CH or N.

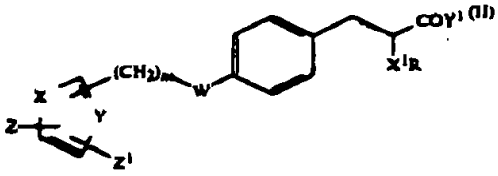
SUMMARY OF THE INVENTION

The present invention is directed to compounds having the formulas



(I)

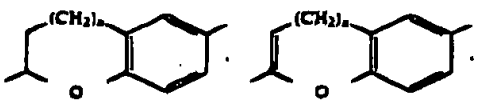
and



(II)

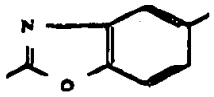
wherein

A is



or

-continued



n is 0 or 1;

m is 0, 1 or 2;

——— represents a bond or no bond;

R is (C_1-C_8)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_8)alkenyl, (C_3-C_8)alkynyl, phenyl, (C_7-C_8)phenylalkyl, (C_2-C_8)alkanoyl, or one of said groups mono- or disubstituted with (C_1-C_2)alkyl, trifluoromethyl, hydroxy, (C_1-C_3)alkoxy, fluoro or chloro;

W is O, CO, CH_2, CHOH or —CH=CH—;

X is S, O, NR^2, —CH=CH—, —CH=N— or —N=CH—;

R^2 is hydrogen, (C_1-C_3)alkyl, phenyl or benzyl;

Y is CH or N;

Z is H, amino, (C_1-C_7)alkyl, (C_3-C_7)cycloalkyl, phenyl, or phenyl mono- or disubstituted with (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

Z^1 is hydrogen or (C_1-C_3)alkyl;

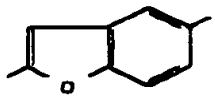
X^1 is O, S, SO or SO_2; and

Y^1 is hydroxy, (C_1-C_3)alkoxy, phenoxy, benzyloxy, amino, (C_1-C_6)alkanoylamino, (C_1-C_4)alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di[(C_1-C_3)alkyl]aminosulfonylamino, or one of said groups mono- or disubstituted with (C_1-C_3)alkyl, trifluoromethyl, hydroxy, (C_1-C_3)alkoxy, fluoro or chloro;

the pharmaceutically-acceptable cationic salts thereof when Y^1 is hydroxy; and

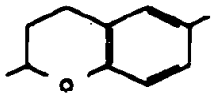
the pharmaceutically-acceptable acid addition salts thereof when the compound contains a basic nitrogen atom.

In the preferred compounds, the dotted line (———) represents no bond. The preferred values of A are



(a benzofuran)

or



(a chroman or 3,4-dihydro-2H-1-benzopyran).

The preferred values of W are O or CO. In their preferred values, X, Y, Z and Z^1 are taken in such manner as to form a 5-methyl-2-phenyloxazol-4-yl group.

In those compounds in which ——— is not a bond, the carbon atom substituted by X^1R and COY^1 is asymmetric, such that these compounds can be either racemic or optically active. Resolution of a racemic form into a pair of optically active enantomers is exemplified below, and the present invention is not to be narrowly